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EXAMINER

CRAIGO, WILLIAM A

ART UNIT	PAPER NUMBER
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1615

NOTIFICATION DATE	DELIVERY MODE
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05/23/2011

ELECTRONIC

Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Notice of the Office communication was sent electronically on above-indicated "Notification Date" to the following e-mail address(es):

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Office Action Summary	Application No. 10/554,157	Applicant(s) OSHLACK ET AL.	
	Examiner WILLIAM CRAIGO	Art Unit 1615	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

- 1) ☒ Responsive to communication(s) filed on 14 March 2011.
- 2a) ☒ This action is **FINAL**. 2b) ☐ This action is non-final.
- 3) ☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

- 4) ☒ Claim(s) 1-47 is/are pending in the application.
- 4a) Of the above claim(s) 1-16 and 32-46 is/are withdrawn from consideration.
- 5) ☐ Claim(s) _____ is/are allowed.
- 6) ☒ Claim(s) 17-31 and 47 is/are rejected.
- 7) ☐ Claim(s) _____ is/are objected to.
- 8) ☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

- 9) ☐ The specification is objected to by the Examiner.
- 10) ☐ The drawing(s) filed on _____ is/are: a) ☐ accepted or b) ☐ objected to by the Examiner.
Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).
Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).
- 11) ☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

- 12) ☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).
- a) ☐ All b) ☐ Some * c) ☐ None of:
1. ☐ Certified copies of the priority documents have been received.
2. ☐ Certified copies of the priority documents have been received in Application No. _____.
3. ☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

- | | |
|--|---|
| 1) <input checked="" type="checkbox"/> Notice of References Cited (PTO-892) | 4) <input type="checkbox"/> Interview Summary (PTO-413) |
| 2) <input type="checkbox"/> Notice of Draftsperson's Patent Drawing Review (PTO-948) | Paper No(s)/Mail Date. _____ |
| 3) <input type="checkbox"/> Information Disclosure Statement(s) (PTO/SB/08) | 5) <input type="checkbox"/> Notice of Informal Patent Application |
| Paper No(s)/Mail Date _____ | 6) <input type="checkbox"/> Other: _____ |

DETAILED ACTION

Status of the Claims

Acknowledgement is made of the response filed 14 March, 2011. In that paper, claims 1, 7, 13, 17, 19, 26, and 32 were amended, claim 18 was cancelled. Claims 17-31 and 47 are pending with claims 1-16 and 32-46 withdrawn due to a previous restriction requirement. Claims 17-31 and 47 are treated on the merits in this action. The following rejections and/or objections are either reiterated or newly applied. They constitute the complete set presently being applied to the instant application.

Amendment

Independent claim 17 has been amended to include the limitation of previously presented claim 18 (now cancelled) "the opioid antagonist is sequestered"; and further amended to include the limitation "wherein the core and the sheath are co-extruded through a co-extrusion die". This amendment necessitates the following modified rejections.

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

(a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negated by the manner in which the invention was made.

The factual inquiries set forth in *Graham v. John Deere Co.*, 383 U.S. 1, 148 USPQ 459 (1966), that are applied for establishing a background for determining obviousness under 35 U.S.C. 103(a) are summarized as follows:

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1. Determining the scope and contents of the prior art.
2. Ascertaining the differences between the prior art and the claims at issue.
3. Resolving the level of ordinary skill in the pertinent art.
4. Considering objective evidence present in the application indicating obviousness or nonobviousness.

This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

Claims 17-31 and 47 are rejected under 35 U.S.C. 103(a) as being unpatentable over Oshlack *et al.* (U.S. Pat. No. 6,696,088) (previously cited).

Oshlack *et al.* ('088) teach an oral dosage form comprising (i) an opioid agonist in releasable form and (ii) a sequestered opioid antagonist which is substantially not released when the dosage form is administered intact, such that the ratio of the amount of antagonist released from said dosage form after tampering to the amount of said antagonist released from said intact dosage form is about 4:1 or greater, based on the in-vitro dissolution at 1 hour of said dosage form in 900 ml of Simulated Gastric Fluid using a USP Type II (paddle) apparatus at 75 rpm at 37°C, wherein said agonist and antagonist are interdispersed and are not isolated from each other in two distinct layers (see Abstract). Oshlack also teaches a method of treating pain in human patients with

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an oral dosage form of an opioid agonist while reducing its misuse by oral, parenteral, intranasal and/or sublingual route (col. 3, line 66 – col. 4, line 3).

An objective of the invention is to provide an oral dosage form containing an effective dose of opioid agonist along with a dose of opioid antagonist which does not change the analgesic efficacy of the opioid agonist when the dosage form is orally administered intact, but which can prevent abuse if the dosage form is tampered with by interfering with the effect of the opioid agonist (col. 3, lines 45-51).

In one embodiment, the invention is directed to an oral dosage form comprising an opioid agonist and naltrexone or a salt thereof in a substantially non-releasable form; wherein the agonist and naltrexone are at least partially interdispersed (see col. 6, lines 14-19).

Oshlack teach that when the antagonist is in the form of multiparticulates coated with a sequestering material, the multiparticulates can be in the form of inert beads coated with the antagonist and overcoated with the material or alternatively in the form of a granulation comprising the antagonist and the material. The multiparticulates can be dispersed in a matrix comprising the opioid agonist or contained in a capsule with the opioid agonist (col. 6, lines 24-32). See also column 5, lines 54-65. Oshlack teaches opioid antagonist particles in a coating that substantially prevents release of the antagonist; the coating or matrix comprising an acceptable hydrophobic material. Suitable hydrophobic materials disclosed include cellulose polymers and acrylic polymers that are insoluble in the gastrointestinal fluids and impermeable to the opioid antagonist (col. 9, lines 31-51); (col. 14, lines 15-20); (col. 19, line 20 – col. 20, line 42).

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These hydrophobic materials read on the hydrophobic materials of instant claims 22 and 23.

Oshlack also teach that the antagonist may be dispersed in a matrix comprising a sequestering material, which substantially prevents the release of the antagonist, and the matrix can be in the form of pellets. The pellets can be dispersed in another matrix comprising the opioid agonist or contained in a capsule with the opioid agonist. In another embodiment, part of the antagonist is in a matrix and/or part of the antagonist is in a coated bead (col. 6, lines 33-41). See also column 5, lines 54-65. The dosage form of the invention can also be provided in the form of compressed tablets, whereby the opioid antagonist is coated with a coating and then mixed with the opioid agonist (col. 9, line 58 – col. 10, line 2). These teachings read on the tablet and capsule of instant claims 28 and 29. See also column 21, lines 35-43.

Oshack teaches that, in certain embodiments of the invention, the substantially non-releasable form of the opioid antagonist is vulnerable to mechanical, thermal and/or chemical tampering, e.g., tampering by means of crushing, shearing, grinding, chewing and/or dissolution in a solvent in combination with heating of the oral dosage form. When thus tampered with, the integrity of the substantially non-releasable form of the opioid antagonist will be compromised, and the opioid antagonist will be made available to be released (col. 8, line 64 – col. 9, line 14). Oshlack teaches that the opioid antagonist which is sequestered, e.g., is not bioavailable when the dosage is administered intact but is bioavailable when the dosage form is tampered with (e.g., in an attempt to misuse the dose of the opioid analgesic) (col. 3, lines 52-58).

Oshlack teaches that the release of the opioid agonist from the oral dosage form is at such a rate that blood (e.g., plasma) concentrations (levels) are maintained within the therapeutic range (above the minimum effective analgesic concentration) but below toxic levels over a period of 8 to 24 hours, preferably over a time period indicative of a twice-a-day or once-a-day formulation (col. 11, lines 10-17).

Preferably, the opioid agonist may be selected from the group consisting of morphine, hydromorphone, hydrocodone, oxycodone, codeine, levorphanol, meperidine, methadone and mixtures thereof (col. 10, lines 3-6); (col. 14, lines 20-54). In certain preferred embodiments of the invention, the opioid agonist comprises hydrocodone, oxycodone or pharmaceutically acceptable salts thereof (col. 10, lines 35-37). These agonists read on those of instant claims 24 and 25. The opioid agonist is provided in sustained release form, which reads on the "controlled release" of opioid agonist instantly claimed (col. 11, lines 10-17); (col. 21, line 44 - col. 22, line 7).

Preferred examples of the opioid antagonist include naltrexone, naloxone, nalmeferene, cyclazacine, levallorphan, pharmaceutically acceptable salts thereof and mixtures thereof (col. 10, lines 7-10); (col. 16, lines 21-25). In certain preferred embodiments of the invention, the opioid antagonist, present in a substantially non-releasable form, comprises naloxone, naltrexone, or pharmaceutically acceptable salts thereof (col. 10, lines 37-40). These antagonists read on those of instant claims 26 and 27.

The sustained-release particles of the opioid agonist have a diameter of about 0.1 mm to about 2.5 mm (col. 22, lines 36-40). The particles of the opioid antagonist

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are about 0.2 to about 2 mm in diameter (col. 9, lines 52-57). These particle sizes read on the "about 0.1 mm to about 3.0 mm" of instant claim 20.

The process for preparing sustained-release matrices are obtained via melt-granulation or melt-extrusion techniques to yield extruded multi-particulates provided within a capsule or extruded multi-particulates provided within a compressed tablet (col. 30, line 8 - col. 32, line 42).

Regarding the limitations of "a plurality of co-extruded second particles comprising a core comprising an opioid antagonist and a sheath which at least partially surrounds the core does not exclude a particle made of a core containing the opioid antagonist and a coating which covers the core, wherein the core and the sheath are co-extruded through a co-extrusion die, and the opioid antagonist is sequestered". Oshlack teaches a particle comprising a core of the opioid antagonist and a coating are sufficient to sequester the opioid antagonist (Oshlack, col. 19, lines 19-40, "opioid antagonist particles may be coated with coating that substantially prevents the release of the antagonist, the coating comprising the hydrophobic material(s)"; see also example 1, naltrexone coated beads; see also example 3, naltrexone extruded pellets). While Oshlack teaches the use of melt-extrusion techniques, Oshlack does not expressly suggest the use of a co-extrusion die as recited in amended claim 17. However, the use of a co-extrusion die does not clearly distinguish the presently claimed subject matter from Oshlack structurally because the result of using a co-extrusion die would be a particle comprising a core with a coating as described in Oshlack. A particle comprising a core which is then coated as taught by Oshlack and a

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particle comprising a core which is coextruded with the coating appear to result in the same product, a particle comprising a coated core containing a sequestered opioid antagonist. Determination of patentability is based on the product itself. The patentability of a product does not depend on its method of production. If the product in the product-by-process claims is the same as or obvious from a product of the prior art, the claim is unpatentable even though the prior product was made by a different process. See MPEP 2113.

Oshlack teaches the release of the second particles being “less than 0.25 mg”, which reads on and falls within the “about 0.5 mg or less” and “about 0.05 mg or less” of instant claims 30 and 31. In the case where the claimed ranges “overlap or lie inside ranges disclosed by the prior art” a prima facie case of obviousness exists. *In re Wertheim*, 541 F.2d 257, 191 USPQ 90 (CCPA 1976); *In re Woodruff*, 919 F.2d 1575, 16 USPQ2d 1934 (Fed.Cir. 1990). Moreover, it is the Examiner’s position that it is deemed obvious to one of ordinary skill in the art to determine suitable or effective levels of release through the use of routine or manipulative experimentation to obtain the best possible results, as these are variable parameters attainable within the art.

Summarily, the prior art clearly teaches and recognizes oral opioid agonist/antagonist combination formulations, whereby the opioid agonist is provided in controlled release form and the opioid antagonist is in sequestered form, in which the antagonist is substantially not released when the dosage form is administered intact. Oshlack *et al.* also teach that the oral dosage form contains an effective dose of opioid agonist along with a dose of opioid antagonist which does not change the analgesic

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efficacy of the opioid agonist when the dosage form is orally administered intact, but which can prevent abuse if the dosage form is tampered with by interfering with the effect of the opioid agonist. Thus, given the teachings of Oshlack *et al.*, the instant invention would have been *prima facie* obvious to one of ordinary skill in the art at the time the invention was made.

Claims 17-31 and 47 are rejected under 35 U.S.C. 103(a) as being unpatentable over Breder *et al.* (U.S. Pat. Appln. Pub. No. 2003/0157168 A1) (previously cited).

Breder *et al.* ('168) teach an oral dosage form comprising (i) an opioid agonist in releasable form and (ii) a sequestered opioid antagonist which is substantially not released when the dosage form is administered intact, such that the ratio of the mean C_{max} of the antagonist after single dose oral administration of the dosage form after tampering to the mean C_{max} of the antagonist after single dose oral administration of an intact dosage form is at least 1.5:1 (see Abstract). Breder also teaches a method of treating pain in human patients and decreasing the abuse of an opioid agonist in an oral dosage form (page 4, ¶ 0050-0053).

Breder teach that when the antagonist is in the form of multiparticulates coated with a sequestering material, the multiparticulates can be in the form of inert beads coated with the antagonist and overcoated with the material or alternatively in the form of a granulation comprising the antagonist and the material. The multiparticulates can be dispersed in a matrix comprising the opioid agonist or contained in a capsule with the opioid agonist (p. 4, ¶ 0047-0049). Breder teaches opioid antagonist particles in a

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coating that substantially prevents release of the antagonist; the coating comprising an acceptable hydrophobic material. Suitable hydrophobic materials disclosed include cellulose polymers and acrylic polymers that are insoluble in the gastrointestinal fluids and impermeable to the opioid antagonist (p. 10, ¶ 0123-0131). These hydrophobic materials read on the hydrophobic materials of instant claims 22 and 23.

Breder also teach that the antagonist may be dispersed in a matrix comprising a sequestering material, which substantially prevents the release of the antagonist, and the matrix can be in the form of pellets. The pellets can be dispersed in another matrix comprising the opioid agonist or contained in a capsule with the opioid agonist. In another embodiment, part of the antagonist is in a matrix and/or part of the antagonist is in a coated bead (p. 4, ¶ 0047). The dosage form of the invention can also be provided in the form of compressed tablets, whereby the opioid antagonist is coated with a coating and then mixed with the opioid agonist (p. 6, ¶ 0071). These teachings read on the tablet and capsule of instant claims 28 and 29. See also (p. 12, ¶ 0137).

Breder teaches that, in certain embodiments of the invention, the substantially non-releasable form of the opioid antagonist is vulnerable to mechanical, thermal and/or chemical tampering, e.g., tampering by means of crushing, shearing, grinding, chewing and/or dissolution in a solvent in combination with heating of the oral dosage form. When thus tampered with, the integrity of the substantially non-releasable form of the opioid antagonist will be compromised, and the opioid antagonist will be made available to be released (p. 5, ¶ 0061). Breder teaches that the opioid antagonist which is sequestered, e.g., is not bioavailable when the dosage is administered intact but is

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bioavailable when the dosage form is tampered with (e.g., in an attempt to misuse the dose of the opioid analgesic) (p. 5, ¶ 0057).

Breder teaches that the release of the opioid agonist from the oral dosage form is at such a rate that blood (e.g., plasma) concentrations (levels) are maintained within the therapeutic range (above the minimum effective analgesic concentration) but below toxic levels over a period of 8 to 24 hours, preferably over a time period indicative of a twice-a-day or once-a-day formulation (p. 6, ¶ 0073).

Preferably, the opioid agonist may be selected from the group consisting of morphine, hydromorphone, hydrocodone, oxycodone, codeine, levorphanol, meperidine, methadone and mixtures thereof (p. 5, ¶ 0068). In certain preferred embodiments of the invention, the opioid agonist comprises hydrocodone, oxycodone or pharmaceutically acceptable salts thereof (p. 6, ¶ 0070). These agonists read on those of instant claims 24 and 25. The opioid agonist is provided in sustained release form, which reads on the “controlled release” of opioid agonist instantly claimed (p. 12, ¶ 0137).

Preferred examples of the opioid antagonist include naltrexone, naloxone, nalmeferine, cyclazacine, levallorphan, pharmaceutically acceptable salts thereof and mixtures thereof (p. 5, ¶ 0068). In certain preferred embodiments of the invention, the opioid antagonist, present in a substantially non-releasable form, comprises naloxone, naltrexone, or pharmaceutically acceptable salts thereof (p. 6, ¶ 0070). These antagonists read on those of instant claims 26 and 27.

The sustained-release particles of the opioid agonist have a diameter of about 0.1 mm to about 2.5 mm (p. 12, ¶ 0142). The particles of the opioid antagonist are about 0.2 to about 2 mm in diameter (p. 5, ¶ 0066). These particle sizes read on the "about 0.1 mm to about 3.0 mm" of instant claim 20.

The process for preparing sustained-release matrices are obtained via melt-granulation or melt-extrusion techniques to yield extruded multi-particulates provided within a capsule or extruded multi-particulates provided within a compressed tablet (p. 16, ¶ 0194-0213). This reads on the "co-extruded" second particles of instant claim 17.

Regarding the limitations of "a plurality of co-extruded second particles comprising a core comprising an opioid antagonist and a sheath which at least partially surrounds the core does not exclude a particle made of a core containing the opioid antagonist and a coating which covers the core, wherein the core and the sheath are co-extruded through a co-extrusion die, and the opioid antagonist is sequestered". Breder teaches a particle comprising a core of the opioid antagonist and a coating are sufficient to sequester the opioid antagonist (Breder, col. 19, lines 19-40, "opioid antagonist particles may be coated with coating that substantially prevents the release of the antagonist, the coating comprising the hydrophobic material(s)"; see also examples 1-2, coating naltrexone particles with a coating that renders the antagonist substantially non-releasable; see also example 5, naltrexone sequestered Naltrexone beads; see also example 6 naltrexone melt extruded multiparticulate formulation). While Breder teaches the use of melt-extrusion techniques, Breder does not expressly suggest the use of a co-extrusion die as recited in amended claim 17. However, the

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use of a co-extrusion die does not clearly distinguish the presently claimed subject matter from Breder structurally because the result of using a co-extrusion die would be a particle comprising a core with a coating as described in Breder. A particle comprising a core which is then coated as taught by Breder and a particle comprising a core which is coextruded with the coating appear to result in the same product, a particle comprising a coated core containing a sequestered opioid antagonist. Determination of patentability is based on the product itself. The patentability of a product does not depend on its method of production. If the product in the product-by-process claims is the same as or obvious from a product of the prior art, the claim is unpatentable even though the prior product was made by a different process. See MPEP 2113.

With regards to the rate of release of the second particles (being “about 0.5 mg or less” and “about 0.05 mg or less” as in instant claims 30/31), it is the Examiner’s position that it is deemed obvious to one of ordinary skill in the art to determine suitable or effective levels of release through the use of routine or manipulative experimentation to obtain the best possible results, as these are variable parameters attainable within the art.

Summarily, the prior art clearly teaches and recognizes oral opioid agonist/antagonist combination formulations, whereby the opioid agonist is provided in controlled release form and the opioid antagonist is in sequestered form, in which the antagonist is substantially not released when the dosage form is administered intact. Breder *et al.* also teach that the oral dosage form contains an effective dose of opioid

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agonist along with a dose of opioid antagonist which does not change the analgesic efficacy of the opioid agonist when the dosage form is orally administered intact, but which can prevent abuse if the dosage form is tampered with by interfering with the effect of the opioid agonist. Thus, given the teachings of Breder *et al.*, the instant invention would have been *prima facie* obvious to one of ordinary skill in the art at the time the invention was made.

Claims 17-31 and 47 are rejected under 35 U.S.C. 103(a) as being unpatentable over Oshlack *et al.* (U.S. Pat. No. 6,696,088) (previously cited) in view of Dyar, US 20020119197 A1.

The teachings of Oshlack are discussed above. While Oshlack teaches oral dosage forms comprising sequestered opioid antagonists in the form of coated particles or particles in a matrix for providing tamper resistant dosage forms, Oshlack does not expressly teach a co-extruded particle comprising a core comprising an opioid antagonist and a sheath which at least partially surrounds the core, wherein the core and the sheath are co-extruded through a co-extrusion die and the opioid antagonist is sequestered as instantly recited.

Dyar is directed to controlled release dosage forms for pharmaceutically active agent comprising a core, in which the agent is dispersed, surrounded by a diffusion limiting sleeve (abstract). Dyar, [0018], teaches the dosage form can be made by coextruding composite products comprising a central core of pharmaceutical agent in a matrix of a controlled release composition, and a surrounding sleeve of a diffusion

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limiting composition. Dyar, Fig. 2, teaches a coextrusion die for making the coextruded pellets.

It would have been prima facie obvious to one of ordinary skill in the art at the time the invention was made to combine the prior art teachings of Oshlack and Dyar according to known methods to provide the predictable result of providing a tamper resistant oral dosage form as claimed. The difference between the teachings of Oshlack and the instantly claimed subject matter is the technique used to sequester the opioid antagonist. Oshlack teaches the concept of providing a dosage form comprising an opioid and an opioid antagonist such that the opioid antagonist is sequestered using known controlled release formulation techniques such as coating particles of the opioid antagonist with a coating material which prevents substantial release when the tablet is taken as directed. Dyar teaches the technique of co-extrusion through a co-extrusion die as a known melt extrusion method for providing controlled release dosage forms of drugs. It would have been obvious to use the technique of coextrusion by extruding the materials through a coextrusion die as taught in Dyar to provide a dosage form wherein the opioid antagonist is sequestered as taught in Oshlack to provide a particle comprising a core comprising an opioid antagonist and a sheath wherein the opioid antagonist is sequestered for formulation as instantly claimed with a reasonable expectation of success. The results would have been predictable because Oshlack teaches conventional coating and matrix extrusion techniques had been used to sequester the opioid antagonist by selection of appropriate hydrophobic excipients. Thus the skilled artisan would have expected that providing a sequestered opioid

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antagonist could be accomplished using equivalent techniques as taught in Dyar. These findings support a conclusion that the claimed invention as a whole would have been prima facie obvious to one of ordinary skill in the art at the time the invention was made.

Accordingly, the subject matter of instant claims 17-31 and 47 would have been prima facie obvious to one of ordinary skill at the time the invention was made, particularly in the absence of evidence to the contrary.

Claims 17-31 and 47 are rejected under 35 U.S.C. 103(a) as being unpatentable over Breder *et al.* (U.S. Pat. Appln. Pub. No. 2003/0157168 A1) (previously cited) in view of Dyar, US 20020119197 A1.

The teachings of Breder are discussed above. While Breder teaches oral dosage forms comprising sequestered opioid antagonists in the form of coated particles or particles in a matrix for providing tamper resistant dosage forms, Breder does not expressly teach a co-extruded particle comprising a core comprising an opioid antagonist and a sheath which at least partially partially surrounds the core, wherein the core and the sheath are co-extruded through a co-extrusion die and the opioid antagonist is sequestered as instantly recited.

Dyar is directed to controlled release dosage forms for pharmaceutically active agent comprising a core, in which the agent is dispersed, surrounded by a diffusion limiting sleeve (abstract). Dyar, [0018], teaches the dosage form can be made by coextruding composite products comprising a central core of pharmaceutical agent in a matrix of a controlled release composition, and a surrounding sleeve of a diffusion

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limiting composition. Dyar, Fig. 2, teaches a coextrusion die for making the coextruded pellets.

It would have been prima facie obvious to one of ordinary skill in the art at the time the invention was made to combine the prior art teachings of Breder and Dyar according to known methods to provide the predictable result of providing a tamper resistant oral dosage form as claimed. The difference between the teachings of Breder and the instantly claimed subject matter is the technique used to sequester the opioid antagonist. Breder teaches the concept of providing a dosage form comprising an opioid and an opioid antagonist such that the opioid antagonist is sequestered using known controlled release formulation techniques such as coating particles of the opioid antagonist with a coating material which prevents substantial release when the tablet is taken as directed by selection of appropriate hydrophobic excipients. Dyar teaches the technique of co-extrusion through a co-extrusion die as a known melt extrusion method for providing controlled release dosage forms of drugs. It would have been obvious to use the technique of coextrusion by extruding the materials through a coextrusion die as taught in Dyar to provide a dosage form wherein the opioid antagonist is sequestered as taught in Breder to provide a particle comprising a core comprising an opioid antagonist and a sheath wherein the opioid antagonist is sequestered for formulation as instantly claimed with a reasonable expectation of success. The results would have been predictable because Breder teaches conventional coating and matrix extrusion techniques had been used to sequester the opioid antagonist by selection of appropriate hydrophobic excipients. Thus the skilled artisan would have expected that

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providing a sequestered opioid antagonist could be accomplished using equivalent techniques as taught in Dyar. These findings support a conclusion that the claimed invention as a whole would have been prima facie obvious to one of ordinary skill in the art at the time the invention was made.

Accordingly, the subject matter of instant claims 17-31 and 47 would have been prima facie obvious to one of ordinary skill at the time the invention was made, particularly in the absence of evidence to the contrary.

Response to Arguments

Applicant's arguments filed 14 March, 2011 have been fully considered but they are not persuasive.

Applicant argues the presently claimed subject matter would not have been obvious in view of Oshlack or Breder because neither reference teaches co-extruded second particles comprising sequestered opioid antagonist which are co-extruded through a co-extrusion die to form a core at least partially surrounded with a sheath as instantly claimed.

This is not persuasive because the plurality of second particles disclosed by the prior art appear to be the same as instantly claimed as discussed above. Even if the presently claimed second particles were co-extruded through a co-extrusion die, insufficient evidence has been provided that shows the different method of production would result in a structural difference. Moreover, even if evidence were presented showing a structural difference it would have been obvious to use a co-extrusion die to provide a plurality of second particles comprising a core comprising an opioid antagonist

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at least partially surrounded by a sheath to sequester the opioid antagonist in view of Dyar.

The Affidavit under 37 CFR 1.132 filed 14 March, 2011 is insufficient to overcome the rejection of claims 17-31 and 47 based upon the rejection under 35 USC 103 (a) over Oshlack OR Breder as set forth in the last Office action because: The evidence presented is a web page which is generally directed to the process of co-extrusion. In argument applicant has generally argued the use of co-extruded techniques results in a different product, however, no clear explanation is given as to how the resulting product would be different in a non-obvious way. Applicant's arguments, in combination with the web page article, alleges coextrusion involves multiple extruders forming layered or encapsulated parts; and the article suggests two or more materials are pressed through the same die to produce a single piece. The previously claimed subject matter did not exclude co-extruding the first and second plurality of particles together into a single dosage form, which reasonably reads on co-extrusion. As presently claimed, this argument is not convincing because the presently claimed subject matter does not distinguish the plurality of second particles which sequester the opioid antagonist from the prior art particles which sequester the opioid antagonist. Oshlack and Breder both teach coated (i.e. encapsulated) beads and drug particles used for the same claimed utility (i.e. to sequester the opioid antagonist). A coated particle or bead appears to be the same or similar product one would get from using a co-extrusion die. The claimed subject matter, when weighed with the affidavit

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provided, does not clearly outweigh the evidence of obviousness of the invention as a whole.

Conclusion

No claim is allowed.

Applicant's amendment necessitated the new ground(s) of rejection presented in this Office action. Accordingly, **THIS ACTION IS MADE FINAL**. See MPEP § 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the date of this final action.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to WILLIAM CRAIGO whose telephone number is (571)270-1347. The examiner can normally be reached on Monday - Friday, 7:30 - 5:00.

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If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Robert A. Wax can be reached on (571) 272-0623. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see <http://pair-direct.uspto.gov>. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

/WILLIAM CRAIGO/
Examiner, Art Unit 1615

/S. TRAN/
Primary Examiner, Art Unit 1615